

University of Khartoum
Graduate College
Medical and Health Studies Board

Prevalence of Latent Tuberculosis Infection among Internally Displaced School Children in Mayo area, Khartoum

By

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A thesis submitted in partial fulfillment for the requirements of the Degree of
Clinical MD in Paediatrics and Child Health.

March ٢٠٠٦

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DEDICATION

To...

The Soul of my sister...

My lovely parents...

My husband...

My sisters, brothers...

&

To the lovely children in mayo...

AKNOWLEDGMENT

I am very grateful to Dr. **Yahia Shakir**, Department of Paediatrics and Child Health Faculty of Medicine, University OF Khartoum, who continuously and kindly supervised and followed my thesis.

I would like to express my thanks to the EPI represented in Dr. Eltayb, the programme manager for sharing the fund of this thesis.

My thanks extend to Dr. Asma Elsony and all the Epidemiology laboratory staff for their help and their input in this thesis.

I would like to acknowledge Dr. Alfraid, the displaced coordinator at the TB programme, and Dr. Bulbek Deing at the DOTS centre in Mayo from the Sudan Council of Churches.

I would like to express my thanks to the Teachers at the schools in Mayo, the Unity basic school, Ibn Zaidon school, Mitadek school and Musaab Ibn Omair basic school

for their cooperation.

I would like to acknowledge the vaccinators Miss. Asaal Fadi Allah (Ahmed Gasim Children Hospital) and Miss. Afaf (Gafaar Ibn Aoof Children Hospital), who joined me the journey with the Driver Altayb.

I do appreciate the effort made by my colleges Dr. Yousif Harb in the data entry, and Dr. Majd for participation in the data collection.

I do thank Dr. Abd Elrahman El Ashaa the Research Director, Primary Health Care unit, Khartoum Ministry of Health for his advice and help.

I would like to thank Mr. Mokhtar and Miss. Samia for the computer work they made.

Thanks for my husband for encouragement and support.

ABSTRACT

Tuberculosis remains a public health problem worldwide. It is a social disease prevalent in population undergoing the stress of poverty, malnutrition and displacement.

This descriptive cross sectional community based study conducted to measure the prevalence of Latent Tuberculosis Infection and associated risk factors among the internally displaced school children in Mayo area in Khartoum (in Mandilla camp and Elwihda area) during the period from 1st of September 2000 to February, 10th 2001.

Tuberculin survey was carried out in four basic schools. 399 schoolchildren in the age group 6-9 years were included in this study. Mantoux test performed with intra-dermal injection of 0.1 ml (2 TU) and reaction measured 3-5 days later.

The mean age of the children in the study is 7.5 years. Females were dominated by males with ratio of 1.2: 1.

Eighty seven percent of the children were vaccinated with BCG and 71.7% of the studied population has BCG scar.

The cutoff points for Latent TB infection were taken at 10 mm and more for the non-vaccinated children and 10 mm and more for the BCG

vaccinated.

The prevalence of Latent TB infection among children without scar is 17.6%, while for the whole 14% of the children were infected; The ARI is estimated as 2.02% which gives an incidence of 100,9/100,000 smear positive cases per year.

Domestic crowding, contact with tuberculous patient and older age are risk factors associated with Latent TB infection in this study. However, the difference was neither significant in relation to gender nor to nutritional status.

Tuberculosis is a preventable disease; improving socioeconomic conditions, reducing crowding, contact investigations and vaccination are strongly recommended for its control.

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LIST OF ABBREVIATIONS

TB:	Tuberculosis
M. Tuberculosis:	Mycobacterium Tuberculosis
HIV:	Human Immunodeficiency Virus.
AIDS:	Acquired Immunodeficiency Syndrome.
PCR:	Polymerase Chain Reaction.
WHO:	World Health Organization.
DOTS:	Directly Observed Treatment Short course.
ARI:	Annual Risk of Infection.
NTP:	National Tuberculosis Programme.
TST:	Tuberculin Skin Test.
TU:	Tuberculin Unit.
CNS:	Central Nervous System.
EPI:	Expanded Programme of Immunization.
NTM:	Non-Tuberculous Mycobacteria.
BCG	Bacille Calmette-Guerin
MSMD:	Mendelian Susceptibility to Mycobacterial
Diseases	
SCC:	Sudan Council of Churches.

CMI:	Cell Mediated Immune response
PPD:	Purified Protein Derivatives
OT:	Old Tuberculin.
MPT:	Multi Puncture Test
MDGs:	Millennium Development Goals
IL:	Inter Leukin
INF:	Interferon
HGIA:	Human gamma-interferon assay.

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CHAPTER ONE

1. INTRODUCTION & LITERATURE REVIEW.

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. It primarily affects the lung and causes pulmonary tuberculosis. It can also affect intestine, meninges, bones and joints, lymph glands and other organs of the body. The disease is usually chronic with varying clinical manifestations. It also affects animals like cattle and known as bovine tuberculosis, which may be communicated to man. Pulmonary tuberculosis is the most important form especially from epidemiological view because patient spread the disease.⁽¹⁾

Tuberculosis remains a worldwide public health problem despite the fact that the causative organism was discovered more than 100 years ago and highly effective drugs and vaccines are available making tuberculosis a preventable and curative disease.⁽¹⁾

The global incidence of tuberculosis is rising, with about 8.8 million new cases⁽²⁾ and 3 million deaths each year from this curable disease⁽³⁾. Almost 1.3 million cases and 400,000 deaths occur among children each year.⁽⁴⁾

The World Health Organization (WHO) estimated that one third of the world's population - two billions- is infected with TB. Infection rates are highest in South East Asia, China, India, Africa and Latin America^(5, 6)

Tuberculosis has reemerged as a major worldwide health hazard with increasing incidence among adult and children. The resurgence of TB during the

last 20 years was a consequence of poverty and immigration; and The main factor blamed to bring TB again is HIV, AIDS. Another major problem contributing to the TB spread is the emergence of drug resistant tuberculosis.⁽⁵⁾ Tuberculosis is especially prevalent in populations undergoing the stress of poor nutrition, overcrowding, inadequate health care and displacement.⁽⁶⁾ Poverty, economic recession, and malnutrition make populations more vulnerable to tuberculosis.⁽⁷⁾

Tuberculosis is a social disease with medical aspect, as Park mentioned. It has also been described as a barometer of social welfare. The social factors include many non-medical factors such as poor quality of life, poor housing conditions, overcrowding, under nutrition, lack of education, large families and lack of awareness of the causes of illness. All these factors are interrelated and contribute to the occurrence of tuberculosis. In fact, tuberculosis began to decline in the western world long before the advent of therapeutic drugs and this has been attributed to improvement in the quality of life.⁽⁸⁾

The problem of TB is acute in the developing countries which account for more than three fourth of the cases in the world.⁽⁹⁾

In Sudan tuberculosis is one of the main public health problems with about 90,000 new smear positive cases per year and 20,000 new TB cases reported in 2004. Health problems are augmented by the civil conflict. Civil wars and its consequences of displacement resulted in a considerable

populations of displaced people living in peripheral areas and camps in the capital Khartoum, The increase in TB associated with war was explained by poor nutrition and over crowding in camps for displaced.

1.1. History of Tuberculosis:

Mycobacterium tuberculosis has been present in the human population since antiquity - fragments of the spinal column from Egyptian mummies from 2400 BCE showed pathological signs of tubercular decay.⁽⁶⁾

The term phthisis (consumption) appears first in Greek literature. Around 460 BCE, Hippocrates identified phthisis as the most widespread disease of the times, and it was almost always fatal.⁽⁶⁾

In 1844, the English physician Benjamin Marten wrote in his publication, *A New Theory of Consumption* that TB could be caused by wonderfully minute living creatures.⁽⁶⁾

The introduction of the sanatorium provided the first really step against TB. Hermann Brehmer, a Silesian botany student suffering from TB, was instructed by his doctor to seek out a healthier climate. He traveled to the Himalayan Mountains and returned home cured. In 1861 he wrote *Tuberculosis is a Curable Disease*. In the same year, he built an institution in Gorbisdorf where, in the midst of fir trees, and with good nutrition, patients were exposed

to continuous fresh air. This setup became the blueprint for the subsequent development of sanatoria, a powerful weapon against tuberculosis. (°)

In 1882, Robert Koch discovered a staining technique that enabled him to see *Mycobacterium tuberculosis*. What excited the world was not so much the scientific brilliance of Koch's discovery, but the accompanying certainty that now the fight against humanity's deadliest enemy could really begin. In 1926, Selman A. Waksman, he and his team were able to isolate an effective anti-TB antibiotic, actinomycin; however, this proved to be too toxic for use in humans or animals. (°)

In November 1944, streptomycin, the antibiotic, was administered for the first time to a critically ill TB patient. The effect was almost immediately impressive. And he made a rapid recovery. The new drug had side effects - especially on the inner ear - but the fact remained, *M. tuberculosis* was no longer a bacteriological exception. (°)

Following streptomycin, p-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962) and rifampin (rifampicin; 1963) were introduced as anti-TB agents. Aminoglycosides such as capreomycin, viomycin, kanamycin and amikacin, and the newer quinolones (e.g. ofloxacin and ciprofloxacin) are only used in drug resistance situations. (°)

1.2. Etiology of Tuberculosis:

The agent of tuberculosis, *Mycobacterium tuberculosis*, *Mycobacterium bovis* and *Mycobacterium africanum* are members of the order Actinomycetales and the family Mycobacteriaceae. The tubercle bacilli are non-spore forming, nonmotile, pleomorphic, weakly gram-positive curved rods about 2-4 µm long. They are obligate aerobes, grow best at 37-41°C, produce niacin and they lack pigmentation.⁽¹⁾ *M. Tuberculosis* is a facultative intracellular parasite ,i.e. it is readily ingested by phagocytes and is resistant to intracellular killing. ⁽¹⁾

The whole mark of mycobacteria is acid fastness. Mycobacteria grow slowly, their generation time being 12-24 hr. isolation from clinical specimens on solid synthetic media usually takes 3-6 wk, and drug susceptibility testing requires additional 4 wk. However, growth can be detected in 1-2 wk in selective liquid medium using radiolabelled nutrients (the BACTEC radiometric system), and drug susceptibility can be determined in an additional 3-5 days. The presence of *M. tuberculosis* in clinical specimens can be detected within hours using PCR that employs a DNA probe that is complementary to mycobacterial DNA or RNA. Data from children are limited, but the sensitivity of some PCR techniques is similar to that for culture. ⁽¹⁾

1.3. Epidemiology of TB infection and disease

Tuberculosis case rate fell during the first half of the 19th century long before the advent of antituberculosis drugs as a result of improving living

conditions. (5) The HIV/ AIDS pandemic has dramatically increased the incidence of this disease. (6)

Environmental factors such as socioeconomic status undoubtedly play the major role in the incidence. Among adults, two-third of cases occurs in males, but there is slight predominance of tuberculosis among females in childhood. It's more common in young adults and children less than 5 years and elderly. The age range 5-14 years is called the favored age because in all human populations this group has the lowest rate of tuberculosis disease. The incidence of drug resistant TB has dramatically increased throughout the world. (7)

In 1998 DOTS (Directly Observed Treatment Short course, the WHO-recommended approach to tuberculosis control based on 5 essential elements) is ranked by the World Bank as one of the most cost effective of all health interventions. The treatment success rate of TB cases in areas where DOTS is operating was 88% compared with 40% in areas that do not use the strategy. (8)

22 countries account for 80% of TB cases worldwide. However, only 3 of the countries, Peru, Tanzania, and Vietnam, have made good progress in controlling TB by using DOTS, while Bangladesh, China, and Congo are making some progress. and the WHO identified 16 countries struggling to control tuberculosis in 1998, Brazil, Indonesia, Iran, Mexico, Philippines, Russia, South Africa, Thailand, Afghanistan, Ethiopia, India, Myanmar,

Nigeria, Pakistan, Sudan, and Uganda.⁽⁷⁾

WHO reports in 2003, there were 4.4 million new cases of TB (14.1/100,000 population) of which 3.9 million (62/100,000) were smear positive and 640,000 (11/100,000) were infected with HIV. In 2003 there were 10.4 million prevalent cases worldwide (240/100,000), of which 6.9 million were smear positive (10.9/100,000). An estimated 1.7 million people (28/100,000) died from TB in 2003, including those co-infected with HIV (229,000).⁽⁸⁾

A total of 182 countries were implementing the DOTS strategy during 2003, two more countries than in 2002. By the end of 2003, 99% of the world's population lived in countries, or part of countries, covered by DOTS. DOTS programmes notified 3.9 million new and relapse TB cases, of which 1.4 million were new smear positive. In total 14.1 million TB patients, and 4.6 million smears positive, were treated in DOTS programmes between 1990 and 2003. The 1.4 million smear positive cases notified by DOTS in 2003 represent a case detection rate of 40%. The rate of treatment success in the 2002 DOTS cohort was 82% on average, unchanged since 2000. As in previous years, the treatment success rate was substantially below average in the WHO African Region (73%) and the WHO European Region (76%). Low treatment success rate in these two regions can be attributed, in part, to the complications of TB/HIV co-infection in the former (Africa) and drug resistance in the latter (Europe).⁽⁹⁾

The United Nations Millennium Development Goals (MDGs) are

stimulating more rigorous evaluations of the impact of DOTS. The MDGs targets directly related to TB control are: by the end of 2005, to detect 70% of new sputum smear-positive cases and successfully treat 85% of these cases; by 2010, to reduce TB incidence, and to halve TB prevalence and deaths rate globally between 1990 and 2010. (9, 10)

As a consequence of DOTS expansion between 1990 and 2003, the global TB prevalence rate fell from 3.9 to 2.5 per 100 000 (including HIV positive TB patients), and by 5% between 2002 and 2003, even though incidence continues to rise. The global mortality rate peaked during the 1990s, and fell at 2.5% (including HIV- positive TB patients) or 3.5% per year (excluding HIV-positive patients) between 2002 and 2003. However, for the strongly adverse trends in Africa, prevalence and death rates would be falling more quickly worldwide. (9)

The WHO analysis of epidemiological trends suggested that the TB incidence rate is still slowly rising globally, but prevalence and death rates are falling. Whether the burden of TB can be reduced sufficiently to reach the MDGs by 2010 depends on how rapidly DOTS programmes can be implemented, and how effectively they can be adapted to meet the challenges presented by HIV co-infection (especially in Africa) and drug resistance (especially in Eastern Europe). (9, 10)

١,٤. Epidemiology of TB in Sudan

١,٤,١. Epidemiology:

An estimated Annual Risk of Infection (ARI) of ١,٨% which gives an incidence of ٩٠/١٠٠,٠٠٠ smear positive cases puts Sudan among the high prevalence countries for TB in the East Mediterranean Region. (١) Despite seemingly overwhelming odds, the DOTS strategy has been successfully commenced in Sudan. (١)

The Sudan National Tuberculosis Programme (NTP) declared DOTS all over in January ٢٠٠٢. The years ٢٠٠٤, ٢٠٠٥ were critical for the NTP for reaching WHO targets for ٢٠٠٥ (of ٧٠% case detection and ٨٥% cure rate). The current level of achievement is about ٣٦% case detection and ٨١% cure rate. (١)

Table (١) The last reported figures of TB cases in Sudan

(Data from the NTP)

Year	٢٠٠٠	٢٠٠١	٢٠٠٢	٢٠٠٣	٢٠٠٤
No. of Cases	٢٥٠,٩١	٢٣٠,٩٩٧	٢٤٠,٥٧٩	٢٥٠,١١١	٢٤٠,٦٤٦

Total number of smear positive cases in ٢٠٠٣ was ١١٠,٠٣ cases and of them ٩٣٥ were in children below ١٥ years of age. In ٢٠٠٤, the total of smear positive was ١١٢٣٦ with ٩١٤ cases in those below ١٥ years. (١)

١,٤,٢. Hospital burden of tuberculosis in Sudan:

Percentage of admission with TB from all inpatients was ١,٠% in ٢٠٠٠,

and ٠,٦% in ٢٠٠٤. In addition, the percentage of death due to the disease of admission: ١١,٢% in ٢٠٠٠, and ١٠,٥% in ٢٠٠٤. (١٧)

Karrar ZA and his colleges published a hospital based study in Khartoum showed that ٧٠% of children admitted with TB had pulmonary TB and case fatality rate of ٦٠%. (١٨)

The civil conflict in Sudan has resulted in a considerable number of displaced populations living in peripheral areas in Khartoum. Health services are provided mainly by Non-Governmental Organizations. TB services are provided through DOTS centers in Sudan Council of Churches (SCC) health centers.

Data from the Sudan NTP about case finding among displaced showed that in Khartoum SCC centers in ٢٠٠٤ a total of ١١٧٢ cases were detected in five centers (Haj Yousif, Jabal Awlia, Mayo Farm, Salama^٢ and Suba Araddi), and ٥٩٦ cases (almost halve) of them were in Mayo. ٦٠٠ smear positive new cases reported at SCC, ٣٥١ of them were in Mayo that is why Mayo was chosen for the study area. (١٩)

١,٥. Pathogenesis:

TB occurs when individuals inhale bacteria aerosolized by infected persons. The organism is slow growing and tolerates the intracellular environment, where it may remain metabolically inert for years before reactivation and disease. The main determinant of the pathogenicity of TB is its

ability to escape host defense mechanisms, including macrophages and delayed hypersensitivity responses. (14)

The infective droplet nucleus is very small, measuring 0.5 micrometers or less, and may contain approximately 1-10 bacilli. 5-100 inhaled bacilli are usually necessary for infection. The small size of the droplets allows them to remain suspended in the air for a prolonged period. Primary infection of the respiratory tract occurs as a result of inhalation of these aerosols. (14)

The risk of infection is increased in small enclosed areas and in areas with poor ventilation. Upon inhalation, the bacilli are deposited (usually in the mid-lung zone) into the distal respiratory bronchiole or alveoli, which are subpleural in location. Subsequently, the alveolar macrophages phagocytose the inhaled bacilli and the bacilli continue to multiply. Thereafter, transportation of the infected macrophages to the regional lymph nodes occurs. Lymphohematogenous dissemination of the mycobacteria to other lymph nodes, the kidney, epiphyses of long bones, vertebral bodies, meninges adjacent to the subarachnoid space, and apical posterior areas of the lungs sometimes occurs. In addition, chemotactic factors released by the macrophages attract circulating monocytes to the site of infection, leading to differentiation of the monocytes into macrophages and ingestion of free bacilli. Multiplication of the mycobacteria occurs within the macrophage at the primary site of infection. (14)

A cell-mediated immune (CMI) response terminates the unimpeded growth of the M tuberculosis 2-3 weeks after initial infection. CD4 helper T cells activate the macrophages to kill the intracellular bacteria with resultant epithelioid granuloma formation. CD8 suppressor T cells lyse the macrophages infected with the mycobacteria, resulting in the formation of caseating granulomas, so most infections are controlled. The only evidence of infection is a positive tuberculin skin test (TST) result. However, the initial pulmonary site of infection and its adjacent lymph nodes (i.e., primary complex or Ghon focus) sometimes reach sufficient size to develop necrosis and subsequent radiographic calcification. (14)

Progression of the primary complex may lead to enlargement of hilar and mediastinal nodes with resultant bronchial collapse. Progressive primary TB may develop when the primary focus cavitates and organisms spread through contiguous bronchi. Lymphohematogenous dissemination, especially in young patients, may lead to miliary TB when caseous material reaches the bloodstream from a primary focus or a caseating metastatic focus in the wall of a pulmonary vein (Weigert focus). Tuberculous meningitis also may result from hematogenous dissemination. Bacilli may remain dormant in the apical posterior areas of the lung for several months or years. Progression of disease because of multiplication of these bacilli may lead to the development of reactivation-type TB. (14)

Most persons infected with M tuberculosis do not develop active disease. In individuals who are immunocompetent, the lifetime risk of developing disease is 8-10%. In certain instances such as extremes of age or defects in CMI (eg, [HIV] infection, malnutrition, administration of chemotherapy, prolonged steroid use), TB may result. For patients with HIV, the risk of developing TB is 7-10% per year.^(1, 2, 3)

Infection with Mycobacterium tuberculosis results in disease in only 8-10% of immunocompetent adults.^{(4) (5)} However, approximately 40% of infants with untreated infection develop disease within 1-2 years. The risk declines throughout childhood. Twenty-five to 30% of children with TB develop extrapulmonary manifestations compared with about 10% of immunocompetent adults.⁽⁶⁾

1.1. Genetic susceptibility to tuberculosis:

Recent researches in TB are studying genetics, and they believe that predisposition to tuberculosis is largely inherited. Before Pasteur's microbial theory of disease, tuberculosis was suspected to reflect an intrinsic host disorder with familial predisposition. This familial theory dominated medical thinking for most of the 19th century. However; Pasteur's microbial theory and Koch's subsequent identification of M. tuberculosis overturned such theories. It was not until 1933 that rigorous genetic epidemiological studies provided strong evidence for the contribution of genetic factors to tuberculosis, with higher

concordance rates of tuberculosis observed among monozygotic than dizygotic twin pairs.⁽¹⁵⁾

Further progress in the understanding of the genetic basis of tuberculosis was achieved from 1996 onwards, with studies of the syndrome known as Mendelian susceptibility to mycobacterial diseases (MSMD). Patients with MSMD are particularly susceptible to weakly virulent mycobacteria (BCG and non tuberculous mycobacteria (NTM) but are resistant to most other infectious agents, with the exception of Salmonella. In the last decade, mutations have been found in five MSMD-causing genes (IFNGR1, IFNGR2, STAT1, IL12B, and IL12RB1). These genes encode proteins that are involved in interleukin (IL)-12/23-dependent, interferon (IFN)- γ -mediated immunity. Twelve distinct genetic disorders responsible for MSMD were diagnosed in >300 patients worldwide in <10 yr, mostly in non-endemic areas. Three MSMD patients with BCG- and/or NTM-induced disease, living in endemic areas, also developed tuberculosis. These patients, who had deficiencies in IFN- γ R1 or IL-12p35 expression, developed tuberculosis between the ages of 2, 8 and 12 years.^(16, 17)

Cases of severe tuberculosis in children with IL-12RB1 deficiency provided proof-of-principle that tuberculosis can be a Mendelian disease. Mendelian predisposition to tuberculosis is not limited to IL-12RB1 deficiency, however, as one child with a partial IFN- γ R1 deficiency suffered from tuberculosis. These observations raise the possibility that a substantial

proportion of children worldwide who have disseminated tuberculosis have a Mendelian predisposition to disease.⁽¹⁹⁾ Pediatric and adult tuberculosis differ markedly in epidemiological features (two distinct peaks of incidence), clinical appearance (disseminated versus pulmonary disease), and pathogenesis (primary infection versus reactivation). These differences probably reflect differences in immunological and genetic control. More genetic studies have focused on adult than on childhood tuberculosis but with less success. No adults with Mendelian tuberculosis have yet been reported.⁽¹⁹⁾

Vaccines that specifically protect genetically predisposed individuals against infection and immunomodulatory drugs that restore impaired immunity are needed to circumvent the inevitable spread of antibiotic-resistant pathogens, including *M. tuberculosis*.⁽¹⁹⁾

1.9. Clinical forms of tuberculosis in children:

- **Primary pulmonary disease:** the primary complex includes the parenchymal focus and the regional lymph nodes. About 90% of lung foci are subpleural, and localized pleurisy is common. The whole mark of primary tuberculosis in the lung is relatively large size of the regional lymphadenitis compared with the relatively small size of the initial lung focus. In most cases the parenchymal infiltrate and adenitis resolve early. The hilar lymph nodes continue to enlarge in some, causing bronchial obstruction and the common sequence is hilar adenopathy, focal

hyperinflation, and then atelectasis. ·^(٤)

The symptoms and signs of primary pulmonary TB is meager considering the degree of radiographic changes often seen. Infants are more likely to experience symptoms. Cough, dyspnea, fever, night sweat and anorexia, difficulty in gaining weight and true failure-to-thrive syndrome are seen. Most cases of tuberculous bronchial obstruction resolve fully with treatment. Occasionally there is residual calcification of the primary focus or regional lymph nodes.^(٤)

- **Progressive primary pulmonary disease:** a rare but serious complication of TB infection with significant signs and symptoms, high fever, severe productive cough, weight loss and night sweats and pulmonary physical signs. The prognosis is excellent with appropriate therapy.^(٤)
- **Reactivation tuberculosis:** seen in adults, and rare in children but may occur in adolescents. The most frequent pulmonary sites are the original parenchymal focus and the apical seedings (Simon foci). This form of disease usually remains localized to the lungs.^(٤)
- **Pleural effusion:** originate in the discharge of bacilli into the pleural space from the pulmonary focus or lymph node. A symptomatic local pleural effusion is frequent in primary tuberculosis that it is basically a component of the primary complex. Tuberculous pleural effusion is infrequent in children younger than ٦ years and rare in those below ١ yr of age. Effusions are usually unilateral but can be bilateral. They are virtually

never associated with a segmental pulmonary lesion and are rare in disseminated tuberculosis. The tuberculin skin test is positive in 70-80% of cases.⁽⁵⁾

- **Pericardial disease:** the most common form of cardiac tuberculosis is pericarditis. It is rare, occurring in 0.5-1% of tuberculosis cases in children. It occurs as direct invasion or through lymphatic drainage. It present with non specific symptoms like fever and weight loss. Pericardial rub or distant heart sounds may be present. Culture of pericardial fluid and granuloma in pericardial biopsy suggest the diagnoses.⁽⁵⁾
- **Lymphohematogenous (disseminated) disease:** tubercle bacilli disseminate to distant organs including liver, spleen, skin and lung apices in all cases of TB infection. The clinical picture produced depends on the quantity of organisms released and the host immune response. The most significant form of disseminated TB is the miliary disease. It usually complicates the primary infection, occurring within 2-6 months of the initial infection. It is most common in infants and young children. Signs and symptoms include fever, anorexia, weight loss, hepatosplenomegaly and lymphadenopathy.⁽⁵⁾ Signs and symptoms of meningitis and peritonitis are found in 20-40% of patients with advanced disease. Choroid tubercles occur in 13-27% of patients and are highly

specific for the diagnosis of milliary TB. ⁽⁵⁾

- **Lymph Node Disease:** often referred to as scrofula, is the most common form of extra pulmonary TB in children. Historically scrofula was usually caused by drinking unpasteurized milk laden with *M. bovis* most cases occur within 6-9 month of initial infection by *M. tuberculosis*. ⁽⁵⁾
- **CNS disease:** CNS tuberculosis is the most serious complication in children and is fatal without effective treatment. It complicates about 1,3% of untreated primary infections in children. It is most common in children between 6 mo and 4 yr. ⁽⁵⁾
- **Bone and Joint disease:** is most likely to involve the vertebrae and the classic manifestation is progression to Pott disease. Skeletal TB is late complication of TB and has become a rare entity since antituberculous therapy becomes available. ⁽⁵⁾
- **Abdominal and gastrointestinal disease:** this occurs through swallowing of respirator secretions or spared from mediastinal or peritoneal lymph nodes. Tuberculous peritonitis which occurs most often in men is uncommon in adolescents and is rare in children. Generalized or localized peritonitis may occur. Rarely the lymph nodes, omentum and peritoneum become matted and can be palpated as a "doughy" irregular non tender mass. Accompanied by ascitis and low grade fever. Tuberculin is usually reactive and diagnosis confirmed by

paracentesis. In Tuberculous enteritis the jejunum and ileum and the appendix are the most common sites. Presentation is with non-specific diarrhea. Tuberculin is usually reactive and diagnosis is confirmed by biopsy. ⁽⁴⁾

- **Genitourinary disease:** renal tuberculosis is rare in children because the incubation period is several years or longer. And tuberculosis of the genital tract is uncommon in both males and females before puberty. ⁽⁴⁾
- **Disease in HIV infected children:** TB in HIV children is often more severe and more disseminated and the diagnosis of TB can be missed because the skin test reactivity may be absent. ⁽⁴⁾
- **Perinatal disease:** symptoms of congenital TB may be present at birth but more commonly begin by the 2nd or 3rd weeks of life. The most common signs are respiratory distress, fever and hepatosplenomegaly. Generalized lymphadenopathy and meningitis occur in 30-50% of patients. The most important clue to diagnosis is maternal or family history of tuberculosis. The infant tuberculin test is negative initially but become positive in 1-3 months ⁽⁴⁾

1.8. Tuberculin Skin Test:

The tuberculin skin test has more than 100 year old history. It was first introduced by Dr. Robert Koch (1890) as a treatment for TB, but failed. The observations that a subcutaneous inoculation of

tuberculin in a tuberculosis patient lead to a local reaction at inoculation site whereas it has no such effect on the non-tuberculous. This laid the foundation for using it for diagnostic purposes.^(1^)

The tuberculin test was discovered by Von Pirquet in 1907.⁽¹⁾ There are three main tests: the Mantoux intradermal test, the Heaf and the Tine multiple puncture tests (MPT). The Heaf test is usually preferred for testing large groups of people because it is quick and easy to perform, reliable and cheap. The Mantoux test is favored when a more precise measurement of tuberculin sensitivity is required. The Tine test (MPT) is considered as unreliable, and therefore is not recommended⁽¹⁾ and should no longer be used in paediatric practice.⁽⁶⁾

The tuberculin test has been the traditional method for detection of infection with tubercle bacilli. Epidemiologists have used it extensively for assessment of tuberculosis situation in different communities.^(1^)

Tuberculin: the test material or antigen is known as tuberculin. There are two major antigens-the old tuberculin (OT), and the purified protein derivative (PPD). PPD is a purer preparation; it gives fewer non-specific reactions and is easier to standardize, it has replaced the OT. PPD is standardized in terms of its biologic reactivity as tuberculin unit (TU). An international standard is

maintained by the WHO against which the potency of other preparations is measured. This standard PPD (PPD-S) has been arbitrarily designated as containing 0.00005 tuberculin units per milligram. (1)

The standard dose (0.1 TU) is defined as the delayed skin test reaction elicited by a 0.00005 mg per 0.1 ml dose of PPD-S. However another large batch of PPD was prepared for use by the WHO designated as RT-23 (1952), the standard low dose for single or first test (0.1 TU) as: 0.00005 mg PPD-S + 0.00005 mg of buffer salt + 0.005% of Tween 80. The Tween 80 is added to prevent adsorbance of the tuberculin to the glass (14).

So, the dosages of PPD are (a) first strength or 0.1 TU, (b) intermediate strength or 0.5 TU, (c) the second strength or 2.5 TU. For routine testing the vaccinating teams in India use 0.1 TU; in some countries 0.5 TU are used. Nearly all truly infected persons react to 0.1 to 0.5 TU. Stronger doses elicit a higher proportion of false positive. (1)

Tuberculin is injected in amount of 0.1 ml intradermally on the mid-volar aspect of the forearm. The injection is given with the standard 0.1 ml tuberculin syringe graduated to hundredth of mm,

fitted with a 26-gauge needle of half an inch length. A satisfactory test should raise a flat pale pea-sized wheal with clear pits of hair follicles and there should be no leakage of tuberculin. The injection of the tuberculin antigen leads to the migration and proliferation of the sensitized T-cell lymphocytes to the test site; they release lymphokines which further attract other lymphocytes and monocytes. These reactions along with increased permeability of the local blood capillaries lead to an induration at the site. The size of the induration is maximal between 48-96 hours after the test. The reading is done by measuring the maximal transverse diameter of the induration. (19)

Tuberculin sensitivity slowly wanes with time. A repeat test may appear to be negative. However a repeat test exerts a booster effect, so that another tuberculin test 1-2 weeks later will give a strongly positive (more than 10 mm) induration result. (1)

1.8.1. Interpretation of tuberculin test:

The hypersensitivity takes about 4-6 weeks to develop after the initial infection and thus infection may be missed in the window

period. The presence of infection is not synonymous to disease and only 10% of infected children break down into disease over their lifetime. (19)

The reaction to the tuberculin may also indicate infection with various non-tuberculous mycobacteria or vaccination with BCG but a significant reaction to the tuberculin skin test merely indicates infection with *M. tuberculosis* (19, 20).

19, 20, 21. Interpretation in children with BCG vaccination:

There is no reliable method of distinguishing tuberculin reactions caused by vaccination with BCG from those caused by natural mycobacterium infections. Therefore, it is usually prudent to consider large reactions to 5 TU of PPD tuberculin in BCG-vaccinated persons as indicating infection with *M. tuberculosis*, especially in countries with a high prevalence of tuberculosis. (21)

Almost all reaction with indurations of 15mm or more in size may be considered attributable to infection with tubercle bacilli irrespective of the presence or absence of BCG scar. Induration of less than 5mm in size usually indicates lack of sensitivity to tuberculin and thus absence of infection neither with tubercle bacilli nor with environmental mycobacteria and 5-15mm can still be

attributed to BCG vaccine. (11)

The reactions of 10-14 mm require more careful interpretation. It could be due to infection with TB, environmental mycobacteria or BCG. It is more likely to be due to M. tuberculosis infection in children who have contact with sputum positive case of pulmonary tuberculosis and in the presence of symptoms, clinical or radiological findings suggestive of tuberculosis. (14)

Large reactions to tuberculin are unlikely due to BCG vaccination because:

- 1) Tuberculin test conversion rates after vaccination may be much less than 10%.
- 2) The mean reaction size among vaccinees is often < 10 mm.
- 3) Tuberculin sensitivity tends to wane after vaccination. (11)(15)

Therefore, the higher the age of the child lesser the probability of the reaction attributable to BCG. (15)

1.8.3. Criteria for positivity by risk group:

Based on the sensitivity and specificity of the purified protein derivative (PPD) tuberculin skin test and the prevalence of TB in different groups, three cut-points have been recommended for defining a positive tuberculin reaction:

>5 mm, >10 mm, and >15 mm of induration. For persons who are at highest risk for developing active TB if they are infected with *M. tuberculosis* (i.e. persons with HIV infection, who are receiving immunosuppressive therapy, who have had recent close contact with persons with infectious TB), >5 mm of induration is considered positive. For other persons with an increased probability of recent infection or with other clinical conditions that increase the risk for progression to active TB, >10 mm of induration is considered positive. These include recent immigrants from high prevalence countries; residents and employees of high-risk congregate settings (including health care workers with exposure to TB and mycobacteriology laboratory personnel), persons with clinical conditions such as silicosis, diabetes mellitus, chronic renal failure, leukemias and lymphomas, carcinoma of the head or neck and lung, weight loss of >10% ideal body weight, gastrectomy, and jejunioileal bypass; and children younger than 5 yr of age or infants, children, and adolescents exposed to adults in high-risk categories. For persons at low risk for TB, for whom tuberculin testing is not generally indicated, >15 mm of induration is considered positive. (11)

1, 8, 4. False negative results:

The reaction to tuberculin may be suppressed in the presence of immunosuppressive states, and in disseminated tuberculosis. Tuberculin size may similarly be diminished in presence of cancer,

Hodgkin disease, sarcoidosis and steroid therapy. During HIV infection, though tuberculin sensitivity is not affected at the initial stages, a greater proportion of individuals show suppression of the test as the CD4 counts decline. (19, 20)

1.1.5. Quantiferon, an alternative to tuberculin

In May 2000, a new in vitro test, QuantiFERON®-TB Gold received final approval from the United States Food and Drug Administration as an aid for diagnosing Mycobacterium tuberculosis infection. This test detects the release of interferon-gamma (IFN- γ) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides representing two proteins present in M. tuberculosis. These antigens impart greater specificity than is possible with tests using purified protein derivative as the tuberculosis (TB) antigen. In direct comparisons, the sensitivity of Quantiferon was statistically similar to that of the tuberculin skin test (TST) for detecting infection in persons with untreated culture-confirmed tuberculosis (TB). The center of disease control (CDC) recommends that Quantiferon may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control. (21)

A study in Australia done to evaluate the sensitivity of a whole blood

human gamma-interferon assay (HGIA, QuantiFERON®-TB) for specific T lymphocyte responses and tuberculin skin testing (TST) for the detection of *Mycobacterium tuberculosis* infection in subjects with culture-proven *M. tuberculosis* disease. Using a defined level of specific IFN- γ production and TST ≥ 10 mm as positive cut-offs, the sensitivity of HGIA was 88% compared to 89% for TST ($p=0.06$). When positive responses in both TST and HGIA were combined, 96% of TB patients were detected. Prior immunization with (BCG) or the type of TB had no effect on the sensitivities of the assays. For those treated for < 5 months, the sensitivities for both assays were 84%, but for those treated for > 5 months the sensitivity of TST (90%) tended to be higher than for HGIA (88%) ($p=0.09$). The study concluded that: HGIA may prove an alternative to skin testing for detecting *M. tuberculosis* infection in certain settings. (33, 34)

3.4. Tuberculin survey and screening for latent TB infection:

The advantages of using the prevalence and annual risk of infection, rather than the prevalence of the disease as epidemiological indicators are that infection is far more prevalent than disease, and it can be measured in children. (35)

Three basic strategies are critical to the prevention and control of TB. The first priority is identifying and completely treating all persons who have active TB. The second priority is contact investigation. The third priority is screening populations at high risk for TB to locate persons infected with TB and giving

complete therapy to prevent the infection from progressing to active, contagious disease. (°)

Decisions to screen particular groups should be based on local epidemiologic data and made in consultation with local health providers to ensure appropriate follow-up, evaluation, and management of persons having TB infection or disease. (°)

Targeted Tuberculin Testing:

Targeted tuberculin testing for Latent TB Infection (LTBI) is a strategic component of tuberculosis (TB) control that identifies persons at high risk for developing TB who would benefit by treatment of LTBI, if detected. Infected persons who are considered to be at high risk for developing active TB should be offered treatment of LTBI irrespective of age. (°)

The following are among the high-risk groups recommended to be screened for TB and TB infection:

١. Close contacts of persons known or suspected to have TB.
٢. Persons infected with HIV.
٣. Persons who have medical risk factors known to increase the risk for disease if infection occurs.
٤. Residents and employees of high-risk congregate settings (e.g., correctional institutions, nursing homes, mental institutions, other long-

term residential facilities, and shelters for the homeless).

- . health-care workers who serve high-risk clients.
- ¶. Some medically underserved, low-income populations.
- ¶. High-risk racial or ethnic minority populations, as defined locally.
- ^. Infants, children, and adolescents exposed to adults in high-risk categories. (⁹)

School-based screening for TB infection among children was started in the 1950s when infection and disease rates were higher than at present.

Well-conducted contact tracing of infectious cases and refugee or immigration testing is more efficient methods than nonselective school-based testing for detecting children who have TB infection. However, targeted testing of high-risk children should be encouraged and may be conducted in the school setting. (⁹)

The choice of study population for Annual risk of infection (ARI) study would be unvaccinated children below 10 years of age in whom the prevalence of mycobacteria other than tuberculosis is minimum. (⁹)

Therefore, the age 0-9 years is the suitable age for tuberculin surveys to measure the prevalence of TB infection in the population, as it is the age when the effect of BCG induced reactivity of the tuberculin wanes, and the acquired reactivity due to environmental mycobacteria is not yet well developed. (⁹)

1.4.1. Tuberculin Surveys in Sudan:

Bayomi reports the Epidemiology of tuberculosis in Sudan since 1900. He reported that the first tuberculin survey conducted in 1920 on 700 schoolchildren, soldiers and hospital patients in Blue Nile province. Positive results obtained were ranging between 9 and 27%. The age distribution of the positive tests ranged between 8 and 30 years. (25)

Three surveys of the annual risk of tuberculosis infection have already been conducted in Sudan 1956, 1976, and a nationwide one in 1986. (26)

The period 1954-60 is a bold figure in the history of tuberculosis control in Sudan, when tuberculin survey conducted and BCG vaccination project applied. The project was aiming to ascertain the pre-vaccination allergy in different age groups in different places in the country, and assist the government in establishing BCG vaccination policy. It also aimed to provide principles of tuberculin testing and BCG vaccination as practical measures in the prevention and control of tuberculosis. (27)

That project carried in two phases. The Southern provinces have the highest positivity rate (64%) while the northern ones have the lowest rate (32%). (28)

56,000 persons were tuberculin tested in the 1956 survey with 0 UT PPD. The results of 1956 of a comparative study to the 1976 showed tuberculin

negativity of 97,3% in 1976 and of 83,4% in 1986 in unvaccinated children 0-6 years. In addition, for those 7-14 years, the negativity was 88,7% in 1986 and 81,8% in 1976. And that showed a decline of infection rate during those 20 years. (7)

The annual risk of infection (ARI %) in North, Central and Eastern Sudan was 1,9 in 1976 (90/100000) and 1,8 in 1986 (90/100000). (7)

The results of the 1986 survey showed an annual risk of infection (ARI) of 1,8 % in the northern part of the country and of 2,4% in the South. (7) A fourth national survey started 2004 is now being conducted.

Zaki conducted tuberculin survey in Red Sea in 1994. Using 2TU; the survey included 1280 unvaccinated children in the age 0-14 years. The cutoff point between positive and negative was 8 mm. and Zaki reported that 34% of the children get infected by 7 years and 44% by 14 years. The overall infectivity was 44% and the ARI 3,4% giving a smear positive cases of (189/100000) population in the Red Sea. (7)

Tuberculin survey was carried in 1679 children (3 month -6 years and school survey for those 7-10 years) in sharg Elneil by Dr. Elnour, 1997, and half of the children showed positive reaction (0 and more). 0-9mm constitutes 40%, while 10mm and more were 11% and the ARI was 2,3 with an estimated incidence of 234 per 100000 populations labeling the area as high risk for tuberculosis. (7)

A recent study (2003) was done in the same area about the BCG efficacy in 1-5 years by Dr. Elhasan. The study showed that 90% of the children were BCG vaccinated, and 73.9% of them had BCG scar. 68.8% of children showed tuberculin reaction ≤ 5 mm, while only 2.0% showed reaction more than 10 mm. (33)

Dr. Diab (1999) studied the prevalence of TB infection among household contact preschool children of smear positive adult tuberculosis patient. A sample of 399 children 5 months to 5 years was screened with mantoux test. Reaction of ≥ 10 mm considered positive in vaccinated and ≥ 10 mm in non vaccinated and malnourished children. The infection rate was significantly high among malnourished and contact of defaulters compared to others. (34)

In Eastern Sudan in 2002, all inhabitants of Marbata village in Atbara River Area underwent both a leishmanin skin test (LST) and a tuberculin test for infection with *L. donovani* and *Mycobacterium tuberculosis*. About 66% were LST-positive, 26% were tuberculin-positive and 2% were positive for both tests. By the age of 10, more than 60% of inhabitants were LST-positive, but <20% were tuberculin-positive. By the age of 30, these percentages increased to 100 and 50%. (35)

1.9.2. Surveys in Africa, Middle East and Worldwide.

Bosman MC and his colleagues in Kenya conducted tuberculin survey in 12 randomly selected districts in the period 1986-1990. Tuberculin testing with

RT23 + Tween 80 was performed in 4,360 primary schoolchildren aged 6-13. Of 14,984 non BCG-vaccinated children, 1,380 (9.2%) had indurations of ≥ 10 mm. Double testing with RT23 and PPD-scrofulaceum in 980 non BCG-vaccinated children revealed a high level of infections due to mycobacteria other than tuberculosis (MOTT). Therefore, the prevalence of tuberculosis infection was based on the sum of 0.7% of the indurations of ≥ 10 mm and all indurations of ≥ 15 mm or more multiplied by two. The prevalence of tuberculosis infection in schoolchildren aged on average 8.5 years was calculated at 0.5%. The corresponding ARTI is 0.6%. The first tuberculin survey conducted by the World Health Organization in Kenya in 1958-1959 found an annual risk of tuberculosis infection (ARTI) of 2.0%. The ARTI has declined by an average 4.6% per year. The tuberculosis problem differs from one area to the next, with the highest prevalence of infection on the coast and in Eastern Kenya and the lowest in Western Kenya (70)

Azbite M in Ethiopia reported that the previous tuberculin survey carried out during the period from 1953 to 1955 revealed the annual risk of infection 3.0%. Between December 1987 and April 1990, health workers administered a tuberculin test to 26,029, 6-to-10-year-old children in 16 districts of Ethiopia to obtain a sample of 45 children who had not received a BCG vaccination earlier. They were able to read the reaction in 99% of the children. 2074 (10.1%) children had a BCG scar and 091 (23%) of them tested positive for

tuberculosis. 20.3 (10.6%) of the 23,690 children who did not have a BCG scar tested positive for tuberculosis. In fact, prevalence was higher in urban areas than rural areas, suggesting overcrowding's effect on transmission. The last tuberculin survey occurred in 1953-1955, at which time the prevalence was much higher than in 1988-1990 (30% vs. 10.6%). In addition, the annual risk of infection was higher (3% vs. 1.4%). Between the 2 surveys the prevalence of tuberculosis fell at a rate of 2.2%/year. Yet, the HIV infection pandemic in Ethiopia threatened that downward trend (7).

In Malawi Salaniponi FM and his colleagues conducted a school survey in twelve randomly selected districts. Children in standard 1-4 and aged 6-11 years were eligible. The prevalence of infection according to various criteria was 9-12% in children without (BCG) scar. The prevalence of reactions of 10 mm or more was lower in girls than in boys, increased with age, and was higher in those with than in those without BCG scar. The annual risk of infection was estimated to be within the range 0.6-1.4%. Annual risk of infection in Malawi was in the order of 1%. This study is expected to provide valuable baseline information for an assessment of the impact of human immunodeficiency virus (HIV) on tuberculosis transmission in Malawi. (7)

Migliori GB performed a tuberculin survey in Arua District- Uganda (577,799 inhabitants, recent return of refugees from Zaire and Sudan) in 1987 prior to the implementation of antituberculosis Chemotherapy and Control

Programme. 1110 students 10 year old without BCG vaccination scar were injected with 0.1 IU of PPD. More than 10 mm of induration were positive. The Infection Rate detected was 1.2% +/- 0.1%. Considering the infection rates found by the Ugandan National Surveys done in 1980 (2.6%) and in 1990 (2.3%), and the slight slope of the curve calculated on those values we have underestimated the real Infection Rate in the district. To avoid this bias the author suggest to include schools in sampling (it is simple and cost-effective) only if the Student's population is likely to be representative of the general population. (74)

Al-Jahdali and his colleagues from Saudi Arabia reported in their study that in countries of the Middle East with moderate to high incidence of active smear-positive pulmonary TB (>20 per 100,000 per year), a positive TST will almost always indicate true TB infection. However, in Middle East countries with very low incidence of active TB (<10 per 100,000 per year), a positive TST will more likely be false positive because BCG vaccination is still routinely given. (75)

Bozkanat E, et al in Turkey performed a Tuberculin skin test screening in a military school in Istanbul city center in high TB burden population. 0.1 TU PPD was injected to every student in the school. Test was repeated after 10 days for negative reactions. Age, sex, the number of BCG scars, smoking and dwelling for last 0 years were asked from the students and their answers were

recorded. More than 10 mm indurations for cases who had no BCG and 15 mm indurations for cases who had BCG were accepted positive. The mean age of the students was 19.72 +/- 1.20. The mean of TST was 12.79 +/- 0.96 mm for all students. In the students who had no BCG, TST positivity was 50%. TB infection prevalence of entire school and AIR were 46% and 3.44% (respectively). That study found that increased number of BCG scar associated with the increased diameter of TST induration. The author thought that AIR values derived from TST conversions done in high risk community by screening annual TST could show all aspects of TB infection risk in those community. (11)

In Iran Ali Sadeghi Hasanabadi studied 1076 healthy children under 6 years who had received BCG at birth with tuberculin test using 0TU PPD. About 71.0% had retained their BCG scar. The average size of tuberculin reactivity was larger in the group with BCG scar than without, the difference being statistically significant ($P < 0.001$). The relative frequency of children showing a negative reaction increased with age; at 4 years about 64% of vaccinated children were negative. There was a positive linear relation between the size of BCG scar and diameter of tuberculin reactivity. After 4 years, tuberculosis infection should be suspected with a positive tuberculin test, especially if the reaction size is > 10 mm. (12)

China has 1.4 million new cases of tuberculosis every year, more than any country except India. A new tuberculosis control project based on short-

course chemotherapy was introduced in half the country in 1991, after a national survey of tuberculosis prevalence in 1990. The China Tuberculosis Control Collaboration conducted another survey in 2000 to re-evaluate the national tuberculosis burden, providing the opportunity to assess the effect of the control project. Children (aged 0-14 years) were suspected of having tuberculosis if they had an induration of 10 mm or greater after a tuberculin skin test. Between 1991 and 2000, prevalence of tuberculosis was reduced significantly in areas of China by use of short-course chemotherapy following the WHO guidelines. ⁽¹⁵⁾

In India Chadha VK and colleagues reported estimates of the prevalence of tuberculous infection among children 1-9 years of age for four defined zones of India from a recently concluded tuberculin survey. These were pooled together and the average annual risk of infection in the country was computed as 1.0%. It was higher in urban areas, at 2.2%, than in rural areas, at 1.3%. ⁽¹⁶⁾

In a study conducted by the National Tuberculosis Institute in India, Chadha VK et al found that 40% of the children aged 1-9 years vaccinated with BCG, elicited either no reaction or a reaction less than 10 mm to 1 TU of PPD RT 23 with Tween 80. And recommended the age 0-9 for tuberculin surveys, irrespective of the BCG vaccination status. As in children aged 1-4 years, the estimated prevalence among those with BCG scar was considerably higher than in those without BCG scar. This difference was small in those aged 0-9 years ⁽¹⁷⁾

(^{٤٥})

Chadha VK and colleges conducted tuberculin survey to estimate annual risk of tuberculosis was in Khammam tribal district in India during ٢٠٠١-٢٠٠٢. ٨٦٣٧ children were test-read, ٢٩٩١ without BCG scar and ٥٤٤٦ with BCG scar. The tests were performed using ITU PPD RT٢٣ cut-off point for infection with tubercle bacilli was considered at ١٢ mm. using this criterion; the prevalence of infection was estimated at ١١,٨% among children without BCG scar and ١٠,٦% among children with BCG scar. This difference was found to be statistically insignificant. ARTI rates computed from the prevalence estimates among children without and with BCG scar were ١,٦% and ١,٥% respectively. It was computed as ١,٥% from the prevalence in the combined group i.e. irrespective of BCG scar status. (^{٤٦})

Survey was done by Kumar in Nepal, ١٩٩٧ in Dharan City that is situated in Eastern Development Region of Nepal where a high percentage of migrated population is residing with very high number of sputum positive cases. The mean age of surveyed population was ١٤,٨ yrs. The Bacilli Calmette Guerin (BCG) coverage (scar rate) was ٣٨,٣%. The Tuberculin positive is ٣٣,٦% with ١٠ mm induration as cutoff line. Annual Risk of Infection (ARI) was ٢,٧% in ٩-١١ age groups and ١,٣١% in ١٢ + age group. This survey is suggestive of tuberculosis being highly prevalent in Dharan. (^{٤٧})

In Kabul, Afghanistan in 2000, Dubuis M, et al administered and read the tuberculin skin test in 89% of registered children. Utilizing a cut-off point of ≥ 8 mm in duration, the estimated prevalence of tuberculous infection was 4.3% and the calculated average ARTI was 0.61%. This indicates a substantial decrease from the estimated ARTI of 2.00% calculated in the 1963 survey. Therefore, there has been a large decrease in the risk of tuberculosis infection in Kabul since the last assessment. And it was reported that the adverse situation in the past decades does not appear to have severely affected the epidemiological situation. ⁽¹⁸⁾

In Hong Kong, there has been nearly universal neonatal BCG vaccination coverage since 1980. Leung CC, et al conducted tuberculin survey among 21 113 schoolchildren aged 6-9 years who were skin tested with one unit of tuberculin (PPD RT-23) during a routine BCG revaccination programme. Using a cut-off point of ≥ 10 mm the ARTI was estimated to be 1.93% (95% CI 1.84 to 2.03) for girls and 1.41% (95% CI 1.33 to 1.50) for boys. ⁽¹⁹⁾

Another study by Bowerman RJ from Taiwan done to investigate the usefulness of the tuberculin skin test (TST) to diagnose TB in BCG-vaccinated populations. It concluded that in eastern Taiwan a positive TST represents either active or latent TB infection rather than past BCG vaccination. Therefore, high BCG vaccination coverage in this region does not appear to limit the

usefulness of the TST as a tool for diagnosing TB.⁽⁹⁾

In Italy Giacchino R and his colleges studied tuberculosis infection and disease in immigrant children. They believe that the increase in TB cases in developed countries is related to different factors, including HIV epidemic and increased number of immigrants from countries with high TB incidence and important socio-economic problems. They carried out a study from January 2001 to December 2002. Mantoux test (5 IU) was performed in immigrant children hospitalized or followed in two children hospitals. The patients were coming from South America (44%) (especially from Ecuador), from Africa (20%), from Eastern Europe (19%), (especially from Middle East and North Africa), from Far East (17%). In 30 cases (13,2%) Mantoux test was positive. Among these latter, 21 presented latent infection, whereas another 9 had tuberculosis disease with pulmonary localization and one of them associated with cervical adenopathy. The prevalence of tuberculosis disease was 2,0% in immigrant children compared to 0,2% in native children. ⁽⁹⁾

Casas Garcia et al, studied the prevalence of tuberculosis in a population from Kosovo sheltered in Catalonia, Spain. They concluded that BCG vaccinated subjects from this population can be considered to be infected by Mycobacterium Tuberculosis as long as the indurations is higher than 10 mm. ⁽⁹⁾

1,10. TB Infection and HIV:

Patients with HIV are among the high risk groups recommended to be screened for TB infection.^(٥٢)

In Thailand INH preventive therapy has been shown in several randomized controlled trials to reduce the risk of developing active TB in tuberculin skin test (TST) or positive HIV infected individuals. CD₄ cell count was significantly associated with TST status. And risk of TST positivity was higher among patients with CD₄ cell counts of ٢٠٠-٥٠٠/mm^٣ and above ٥٠٠/mm^٣ when compared to patients with CD₄ cell counts of less than ٢٠٠/mm^٣.^(٥٤)

١,١١. BCG vaccination in Sudan:

The national policy is to give BCG at birth or at the first visit to the health services. Age recommended for vaccination is from birth to ١ year, and is usually at or below ٢ month as a single dose.

BCG coverage for less than ١ year in Sudan ١٩٩٨ was ٧٩,٩ and in ٢٠٠٤ = ٧١%.

The states with the burden of civil conflict in the Southern Sudan (Jongli, Equatorial and N Bahr Alghazal) and recently the Western Sudan (West Dar For) had BCG coverage < ٥٠% in ٢٠٠٤, although W. Dar For had achieved ٨٨% coverage in ١٩٩٩. And most of the displaced populations are from these states.^(٥٥) About the study area the BCG coverage in Gabal Awlia locality in ٢٠٠٤ was ٨١,٧ %.^(٥٦)

Table (٢) The Sudan BCG coverage< ١ year.

(Data from the EPI, Federal Ministry of Health)

Year	١٩٩٨	١٩٩٩	٢٠٠٠	٢٠٠١	٢٠٠٢	٢٠٠٣	٢٠٠٤
BCG Sudan coverage %	٧٩,٩	٩٢,١	٦٦,٣	٧٠,٨	٦٨,٣	٧٣	٧١
Khartoum State	١٦٢	١٦٢,٥				٨٠	٨٢
N B Elgazal State.	٥	٩,٧				٦	١٦
Jungli State.			٣,٦			١٧	٢٠
West Darfor State.	١٤	٨٨,٢	١١,١			٥٣	٤١

JUSTIFICATIONS

١. Tuberculosis remains a major public health problems and the global incidence of TB is rising.
٢. As reported by the Sudan National Tuberculosis Programme, Sudan is among the high prevalence countries of TB in the Middle East.
٣. The children living in peripheral areas in Khartoum most of them were originally displaced from the Southern and Western Sudan. Such population with poor living conditions, poverty, crowding are more prone to infectious disease. TB is one of the important infectious diseases worldwide.
٤. Tuberculosis is a social disease with medical aspect. It has also been described as a barometer of social welfare. known to be prevalent among population suffering from poverty, and displacement. Such population is among the high-risk population recommended to be screened for TB.
٥. The states affected by civil conflict in the south and recently the west have BCG vaccination coverage below ٥٠% in ٢٠٠٤. And this is another factor makes such population worth screening for TB infection and disease.

OBJECTIVES.

General objectives:

To assess the prevalence of Latent TB infection among internally displaced school children in Mayo area in Khartoum, ٢٠٠٥.

Specific objectives:

- ١- To determine the prevalence of latent tuberculosis infection in Mayo using the tuberculin test among schoolchildren, considering the BCG vaccination status.
- ٢- To assess the relationship between Latent TB infection and the following risk factors:
 - a) Socio-economic factors
 - b) Nutritional factors.

CHAPTER TWO

٢. METHODOLOGY

٢,١. Type of the study:

This is a descriptive cross sectional, community based study.

٢,٢. Study area:

Mayo area (or Elnasr) is located to the south of Khartoum. It is governed by Gabal Awlia locality. The total population is about ٤٢٠,٠٠٠. Mayo (Elnasr) unit is divided into nine sectors. This study was conducted in two of these sectors Elwihda and Mandilla (which is also called Mayo Elsalam). Elwihda has a population of ١١٦,٥٥٠. While the population in Mandilla is about ٦٥,٩٠٠. Elwihda is started to be constructed and planned, however Mandilla is classified as a camp area. The water supply of both areas is from well. Water is availed to the population through hand pumps. These hand pumps are distributed through the area and people collect water from there to their homes. About the sanitation in both of the areas is in form of simple pit latrines. (٥٧)

Most of the populations are from Bahr Gazal State, Upper Nile, Equatorial, Nuba Mountains and Darfor. (٥٧)

Health services provided through Governmental and non Governmental Organizations (NGOs). TB services are provided in DOTS at Sudan Council of Church (SCC) health center. (٥٧)

٢,٣. Duration of the Study: This study was conducted during the period from

the 1st of September 2000 to Feb, 10th 2001.

2.4. Study population and sampling technique:

This study included 399 school children aged 6-9 years.

Sample size:

$$N = Z^2 Pq / d^2$$

$$P = \text{Prevalence} = 0.00$$

$$q = 1 - p$$

Sample size is 380 children.

Sampling techniques:

Multi- Stage Sample:

Defined as a procedure in which groups of individuals themselves are the unit of sampling. In a survey covering a district, province or country an initial sample may be taken from units of the population such as villages. The villages listed and a random sample of the required number selected. Then a listing of individuals within the chosen villages is made and a sample taken from them. This is a two-stage sampling. The same procedure of sub-dividing the population into progressively smaller units may be extended to three or more stages as required. This method of sampling is has the advantages that a listing of persons is only required for the relatively small unit from which the final selection is made. (1)

There are 16 basic schools in the study area with a population of 1228.

pupils.^(°)

Schoolchildren 6-9 yrs were involved in the study.

From the list of 16 schools in the area, two schools were excluded one for boys and the other for girls. The remaining 14 schools are for both girls and boys. From those, four schools selected for the study by simple random sampling. The number of pupils 6-9 years in the selected schools ranged between 90-130 children in each.

The pupils within the selected school aged 6-9 years in the 1st and 2nd grades listed by the teacher. Number 1 is the list was the first to start with and selection continued onward according to the list.

2.5. Inclusion criteria:

Children 6-9 years in the selected schools.

2.6. Exclusion criteria:

- Children found ill at school on the day of testing.
- Children whose parents or caregiver did not attend school on the day of testing.

2.7. Research team:

- 1- The author
- 2- Two vaccinators expert in administering tuberculin and measuring the indurations.
- 3- One teacher from each school was involved in contacting parents,

providing list of pupils with ages and gender.

٢,٨. Input of the author:

The input of the author was to:

- ١- Design the study and questionnaire.
- ٢- Make necessary contacts and obtain permissions from the authorities.
- ٣- Avail the tuberculin and vaccine carriers and insure good storage and proper temperature.
- ٤- Obtain consent from parents and fill the questionnaire.
- ٥- Measure the weight and height for all the children in the study.
- ٦- Perform physical examination for the children whom tuberculin skin test is positive.
- ٧- Perform tuberculin test and read results with the vaccinators, and supervise the vaccinators.

٢,٩. Research tools:

٢,٩,١. Consents:

- Written approval taken from the Ministry of Education.
- Written approval taken from the Sudan Council of Churches.
- Verbal consents taken from the parents or caregivers of the children in the study.

٢,٩,٢. A pre-coded questionnaire:

All students in the study had questionnaire completed. Containing: Personal

data (age, gender, place of birth, duration of residence in Mayo area), parent education and occupation, monthly family income, number of persons per room, history of contact with tuberculous patient, BCG vaccination status, and history of symptoms suggestive of TB and history of drugs if any are used. Physical examination (including weight and height using stadiometer) performed for all the children in the study.

Presence or absence of the BCG scar and the tuberculin test reading.

٢,٩,٣. The Tuberculin:

Tuberculin RT- ٢٣ with Tween ٨٠ from Vacsera (Egypt) was used. It is provided in liquid form in two milliliter vials, with concentration of ٥TU per ٠,١ ml.

The tuberculin was availed by the Central Medical Supplies. It costs ٣٥٠٠ SD per one vial of tuberculin.

The tuberculin was kept at ٢-٨ C and transferred to the field of the study in vaccine carriers.

٢,٩,٤. Mantoux test:

- ١ ml syringes with ٢٧ gauge graduated in ١٠٠ of milliliters were used to apply the test.
- The volar aspect of the left forearm is inspected. The skin is slightly stretched and the needle inserted intradermally.

- The 0.1 ml is injected to form a pale raised area with pits of hair follicles.
- Indurations measured 48hr- 96hrs later; the site of injection is inspected in good light and then palpated. The palpable induration is lined in its transverse diameter with a pen and the space between the two lines (induration and not erythema) measured by a transparent ruler in millimeters and the number is reported.
- When no induration palpated the number reported is (0).

The cutoff point of ≥ 10 mm for vaccinated and ≥ 15 mm for the non-vaccinated considered due to Latent Tuberculosis Infection.

4.1.4. Ethical consideration

- An approval letter was taken from the Ministry of education, and written consent from school directors in the study area.
- Parents (mainly mothers) were requested by teachers to attend school in the day of tuberculin test, the procedure was explained and verbal consent taken by the author.
- Parents were informed about the procedure and the expected indurations or even necrosis.
- Children who test positive were referred to the nearest hospital, for further management.

4.1.5. **Data entry and analysis:** data was entered and analyzed using the SPSS

(Statistical Package for Social Sciences) computer programme. Cross tabulation between variables was done. The χ^2 test was used with P value at 95% confidence level was used as the test of significance, probability value of < 0.05 was considered significant.

2.12. Funding: the study was funded by the author with contribution from the EPI, Federal Ministry of Health.

CHAPTER THREE

3. RESULTS

416 children were included; however 17 were excluded as they were not available while reading the result of the Mantoux test. Full records of 399 children were analyzed with the following results.

3.1. Sociodemographic characteristics of the study group:

3.1.1. Gender distribution:

In this study males were 221 (55.4%), and the females were 178 (44.6%) with males to Females ratio of 1.2:1, as shown in (Fig 1).

3.1.2. Age groups:

The mean age was 5.42 years. Different age groups are shown in (Fig 2).

Fig (1) Gender distribution among study population n= (399) .

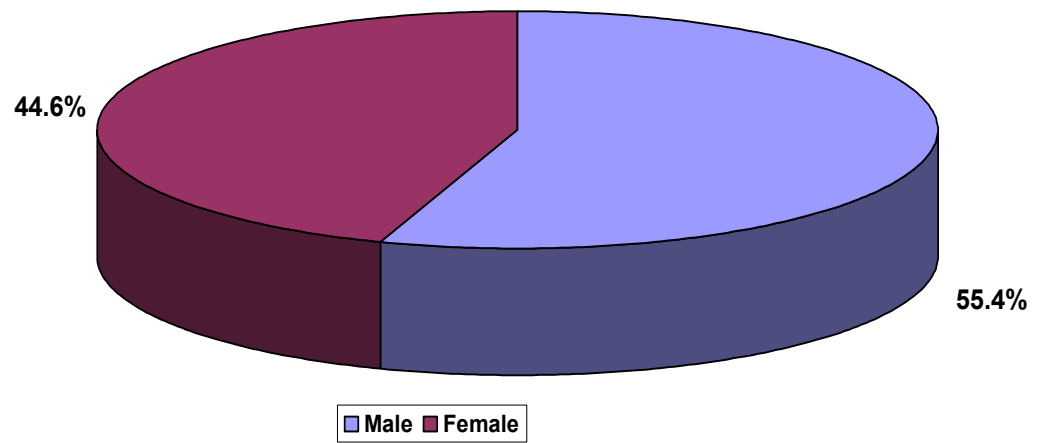
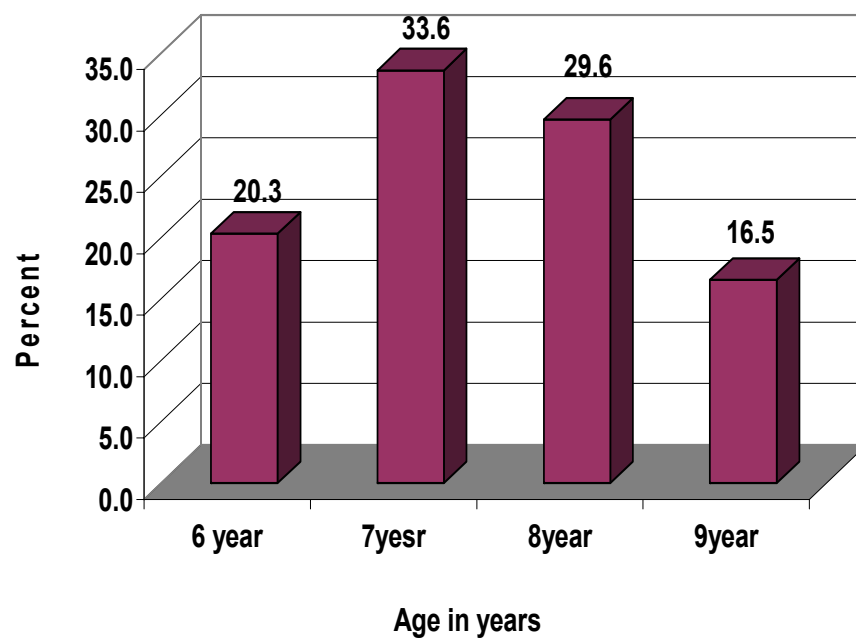


Fig (2) Age distribution in the study population n= (399) .



3.1.3. Place of birth:

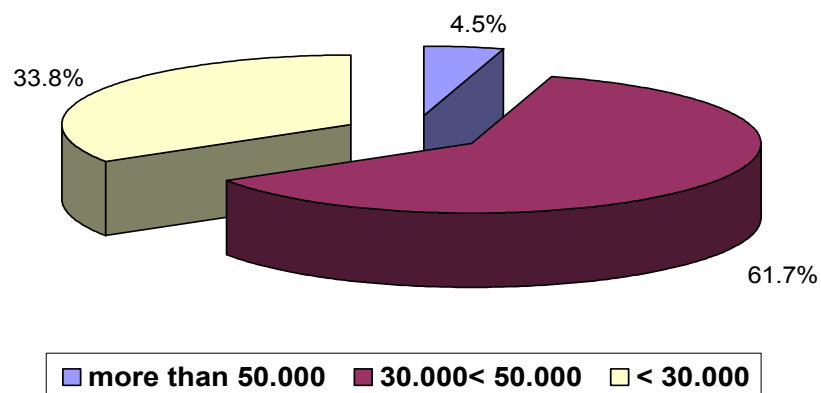
Although almost all of the families were originally from the south and the west, 90% of them have been residing in Mayo before the birth of their children who are included in this study, while only about 10% of the children were born in distant States in the Southern, Western and Northern Sudan and were new residents in Mayo. This concluded that the population studied was originally internally displaced; however most of them have been settled in Mayo for more than five years.

3.1.4. Monthly Family income:

It was difficult for most of the parent to provide a specific number for their monthly family income, as most of them are laborers collecting money on a daily base, which differ from one day to another, and so they gave approximate figures in ranges.

66,7% of the children were from families with a monthly income in the range of 30,000 - 50,000 SD, 33,3% has <30,000 SD and only 0% has > 50,000 SD per month as shown in (Fig 3).

Fig (3) Family monthly income in Sudanese dinarrs among study group n= (399) .



3.2. Certain characteristics of the children in the study:

3.2.1. BCG vaccination status among the children:

History of BCG vaccination was reported in 348 (87,2%) children documented either by scar or vaccination card or both. While 30 (8,8%) children have never been vaccinated and 16 (4%) children had no BCG scar and their vaccination status was not known. This is represented in (Fig 4).

3.2.2. Age at BCG vaccination of the children:

Almost all the vaccinated children (98,6%) had their BCG given within the first two month of life, either at birth or at 1 week with the first doses of OPV and DPT. Only 1,4% had had their BCG between three and six month.

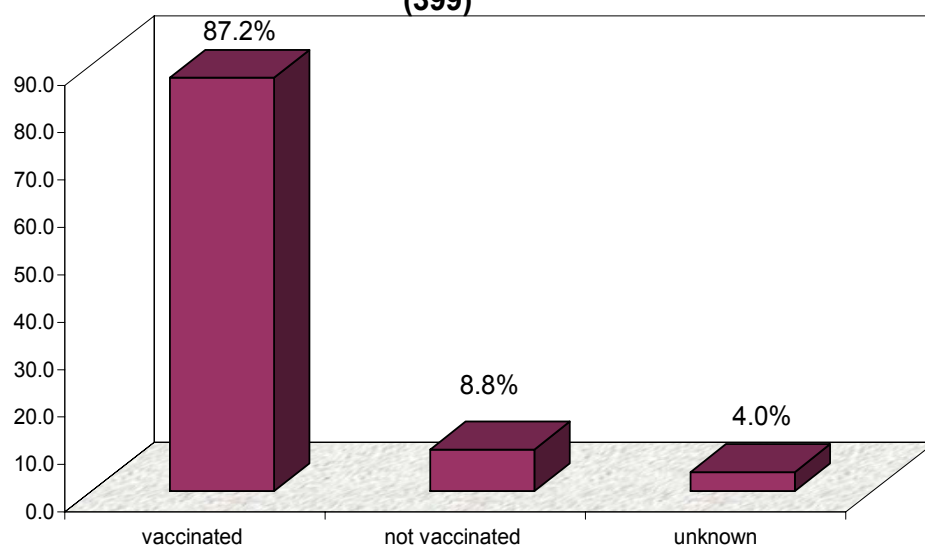
3.2.3. BCG scar in relation to history of vaccination:

Among the vaccinated (348 children), 286 (82,1%) children have BCG scar.

3.2.4. BCG scar rate among the children in the study:

Two hundreds and eighty six of the children (82,1%) have BCG scar. Among the 348 children (98,6%) without BCG scar, 28 children (8,0%) were vaccinated but they did not develop scar, 34 children (9,8%) had never been vaccinated and 16 children (4,6%) have their vaccination status unknown.

Fig (4) History of BCG vaccination among the study population n= (399)



3.2.5. Body Mass Index (BMI):

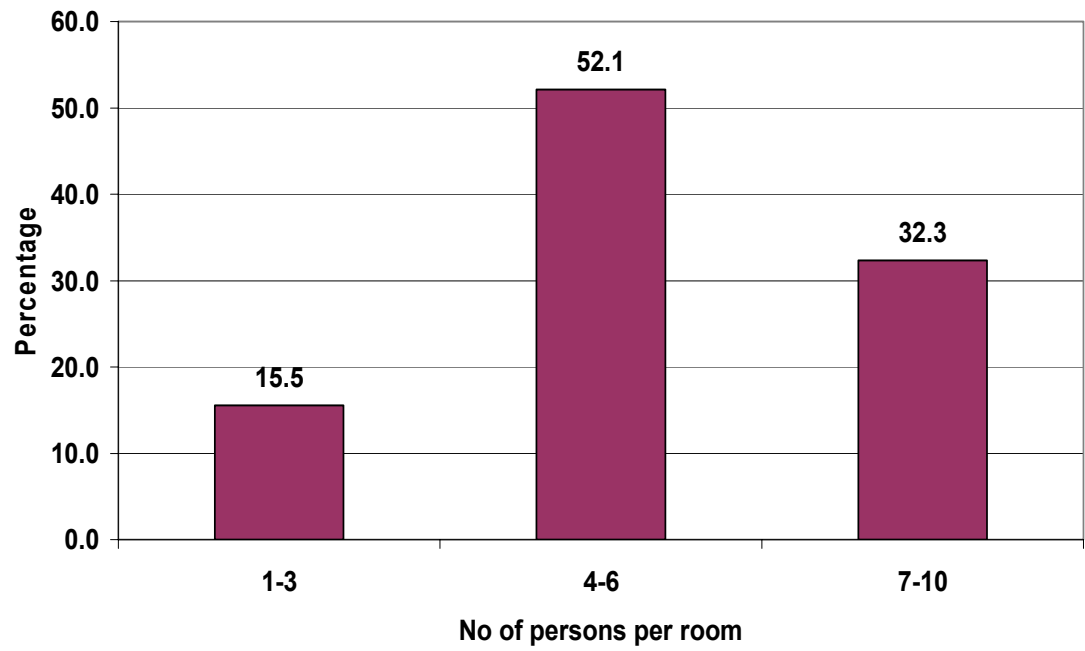
The children were weighed without shoes and their height measured while standing straight on the stadiometer. Body mass index was calculated for every child and plotted in chart from the National Center for Health Statistics (NCHS).

48 children (12,0%) have BMI below the third centile for their age. While the rest were within normal range BMI (88,0%).

3.2.6. Number of persons per room:

When more than three persons per room is considered as domestic crowding, then most of the children 337 (84,0%) are living in crowded homes and only 62 (10,0%) are residing with three persons or less per room as shown in (Fig 5).

Fig (5) number of persons per room among study population n= (399) .



3.3. Result of the Mantoux test:

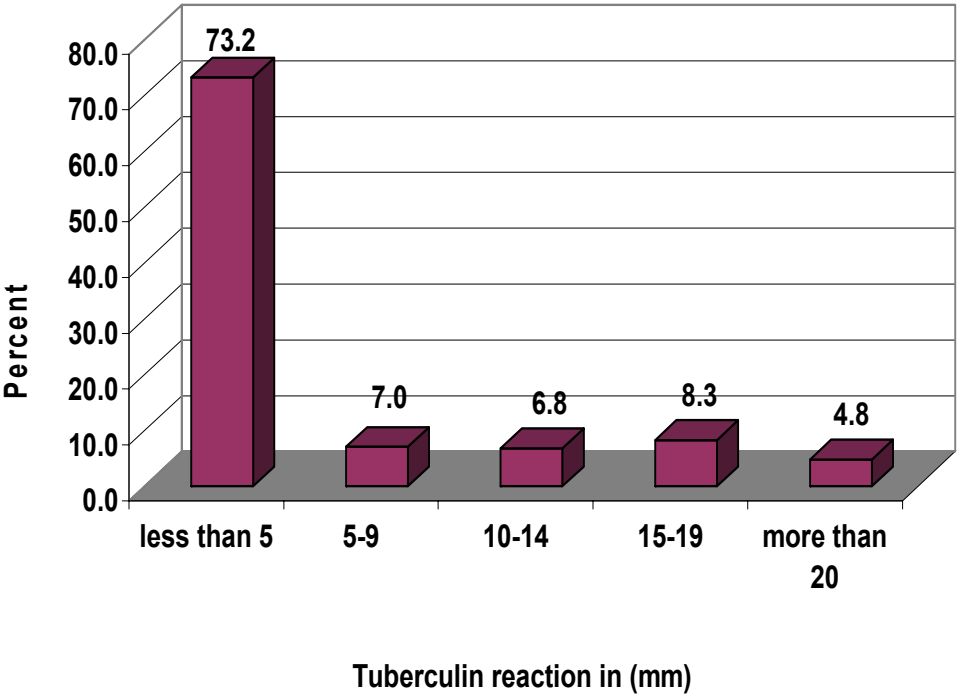
3.3.1. Tuberculin reaction among the study population:

Two hundred and ninety two children (73,1%) had < 5mm indurations, 28 children (7,0%) had 5-9 mm, 22 children (6,8%) had 10-14 mm, 33 children (8,3%) had 15-19 mm and 19 children (4,8%) had reaction of 20 mm and more. This is shown in (Fig 6). Reaction at 20 mm and more were found in 19,9% of the total children in the study.

3.3.2. Tuberculin reaction among different age groups:

Tuberculin reaction was different among different ages with reaction less than 5 mm indurations represented more among children at 1 years and the reactions of 15mm are more prevalent among children of 4 years old, and this difference is statistically significant as shown in (Table 7).

figure (6): tuberculin reaction in(mm) among the study population n= (399)



**Table 3: Tuberculin reaction among different age group in the study population.
(n=399)**

Tuberculin reaction in (mm)	Age in yrs					
	<u>1-7 yrs</u>		<u>8-9 yrs</u>		<u>Total</u>	
	No	%	No	%	No	%
Less than 0	160	74,8	132	71,7	292	73,1
0-9	14	6,0	14	7,6	28	7,0
10-14	21	9,8	6	3,3	27	6,8
15-and more	20	9,3	32	17,4	52	13,1
Total	215	100	184	100	399	100

$$\chi^2 = 31,610$$

$$P. \text{ value} = .002$$

3.3.3. Tuberculin reaction in relation to the BCG scar:

There was no significant difference in tuberculin reaction among the children with and without BCG scar as shown in (Table 4).

3.4. Prevalence of latent tuberculosis infection:

Considering 10 mm or more for those not vaccinated and 15 mm and more for vaccinated as cutoff point for Latent TB infection, 56 children (14.0%) were infected with TB and 343 (86.0%) were not infected, so the prevalence of infection: 14.0% as represented in the Pie chart in (Fig 5).

While among the children without BCG scar when considering 10 mm and more as positive: the positivity rate is 14.6%, so the prevalence of latent TB infection among children without BCG scar is 14.6%.

Table 4: Tuberculin reaction in relation to BCG scar among the study population. (n=399)

<u>Tuberculin reaction</u>		<u>BCG scar</u>				
<u>(mm)</u>	<u>Present</u>		<u>Not present</u>		<u>Total</u>	
	No	%	No	%	No	%
Less than 10	210	73.4	82	22.6	292	73.2

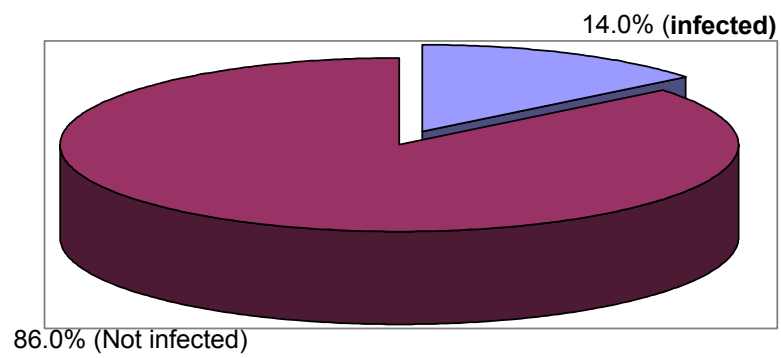
0-9	17	0,9	11	9,7	28	7,0
10-14	21	7,4	6	0,3	27	6,8
15-19	24	8,4	9	8,0	33	8,3
More than 20	14	4,9	0	4,4	19	4,8
Total	286	100	113	100	399	100

$$\chi^2 = 2,217$$

$$P. \text{ value} = .196$$

Fig (7) Prevalence of TB infection among the study population

n=(399)



3.2. Factors affecting the tuberculin reaction and the prevalence of Latent TB infection:

3.2.1. Relation between latent TB infection and age groups:

Two (3.0%) of the children of 1 years old were infected, 20 (14.9%) of children aged 2 years, 19 (16.1%) of those aged 3 years and 10 (22.7%) among children of 4 years. This represents that infectivity increases with increasing age, and this was statistically significant difference $P < 0.05$ (Table 2).

3.2.2. Gender in relation to Latent TB infection:

Thirty four out of 221 male children (15.4%) were infected with TB while 22 out of the 144 female children (15.3%) were infected. And this was statistically not significant, $P = 0.88$, i.e. no specific gender found to be a risk factor of Latent TB infection in this study (Fig 1).

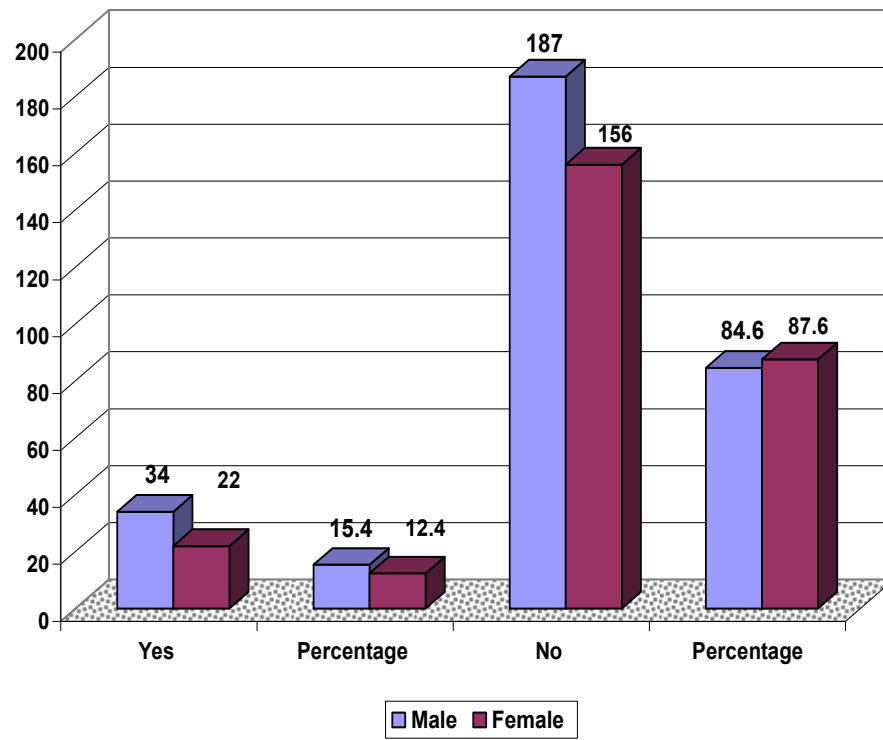
Table 2: Latent TB infection in relation to the age among study population (n=339)

Latent TB infection	Age (years)									
	6		7		8		9		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Yes	2	2,0	20	14,9	19	16,1	10	22,7	51	14,9
No	79	97,0	114	85,1	99	83,9	51	77,3	339	86,0
Total	81	100	134	100	118	100	61	100	339	100

$\chi^2 = 13,619$

P. value = .002

Fig (8): Gender in relation to TB infection among study population.(n=399)



٣,٥,٣. Monthly income in relation to the Latent TB infection:

The relation between the monthly income and Latent TB infection is shown in (Table ٦).

٣,٥,٤. Contact with TB in relation to Latent TB infection:

Thirty four children (٦٠,٧%), out of the ٥٦ infected children, had history of contact with TB patient either household (٢٣,٢%) or neighbor (٣٧,٥%). ٢١ children (٣٧,٥%) of the infected has no history of contact and ١ child (١,٨%) had infection with unknown contact. The relation between history of contact and Latent TB infection was significant $P < ٠,٠٠٠$ (Table٧).

Table ٦: Monthly family income in relation to Latent TB infection. (n=٣٩٩)

Monthly income SD	Latent TB infection					
	<u>Yes</u>		<u>No</u>		<u>Total</u>	
	No	%	No	%	No	%
More than ٥٠٠٠٠	٧	٧,١	١٤	٤,١	١٨	٤,٥
٣٠٠٠٠<٥٠٠٠٠	٣٧	٦٦,١	٢٠٩	٦٠,٩	٢٤٦	٦١,٧
< ٣٠٠٠٠	١٥	٢٦,٨	١٢٠	٣٥,٠	١٣٥	٣٣,٨
Total	٥٦	١٠٠	٣٤٣	١٠٠	٣٩٩	١٠٠

Table ٧: History of contact with TB patient in relation to Latent TB infection. (n=٣٩٩)

Contact with TB	Latent TB infection					
	<u>Yes</u>		<u>No</u>		<u>Total</u>	
	No	%	No	%	No	%
Contact(household or neighbor)	٣٤	٦٠,٧	٤٩	١٤,٢	٨٣	٢٠,٨
No contact	٢١	٣٧,٥	٢٧٧	٨٠,٨	٢٩٨	٧٤,٧
Unknown	١	١,٨	١٧	٥,٠	١٨	٤,٥
Total	٥٦	١٠٠	٣٤٣	١٠٠	٣٩٩	١٠٠

$$\chi^2 = ٧٥,٦٣٧$$

$$P. \text{ value} = .٠٠٠$$

३,०,०. Body mass index (BMI) in relation to Latent TB infection:

Among the children with BMI below the third centile १६,१% were infected, while among the children with BMI appropriate for age १३,१% were infected. This is represented in (Fig १).

३,०,१. Number of persons per room in relation to Latent TB infection:

There is significant relation between the number of persons per room and the presence of TB infection in the study population. P value .०१३ as shown in (Table १).

figure (9): Body mass index in relation to TB infection n=(399)

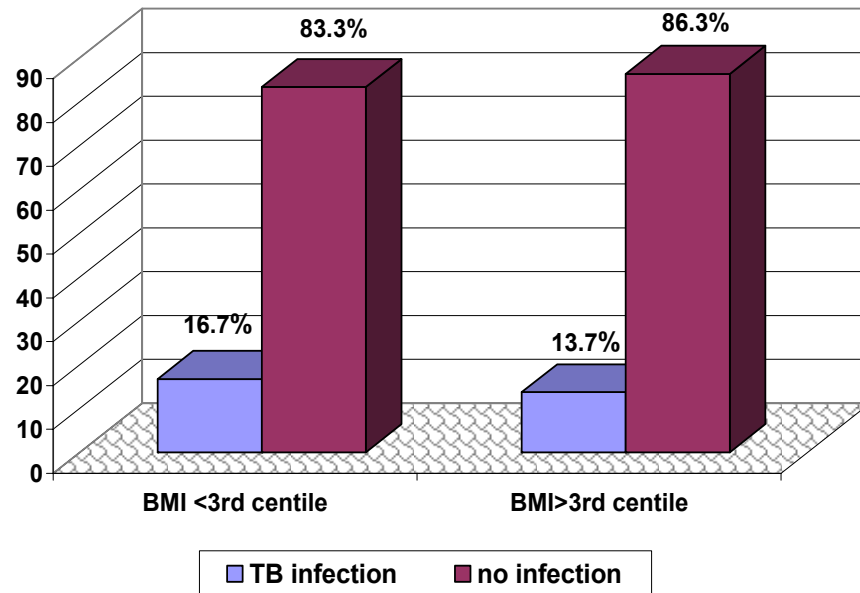


Table 1: Number of persons per room in relation to Latent TB infection (n=399)

No. of Person per room	Latent TB infection					
	<u>Yes</u>		<u>No</u>		<u>Total</u>	
	No	%	No	%	No	%
1-3	7	12,0	55	16,0	62	15,0
4-6	22	39,3	186	54,3	208	52,2
7 to 9	27	48,2	102	29,7	129	32,3
Total	56	100	343	100	399	100

$$\chi^2 = 7,032$$

$$P. \text{ value} = .023$$

٣,٦. Factors contributing to the BCG vaccination among the study group:

٣,٦,١. Place of birth in relation to BCG vaccination:

The difference in the history of BCG vaccination among the children who were born in Mayo and those who were born in the South and Western States was statistically significant (P value ٠,٠٠٠) i.e. The children who were not born in Mayo were more likely to be not vaccinated. And birth in Khartoum gives better chance of vaccination. The same relation is seen when considering the BCG scar in relation to the place of birth.

Table ٩ shows that among those born in Mayo (i.e. in Khartoum state) ٢٥٩ children (٩٢,٥%) were vaccinated, ١٠ children (٣,٦%) were not vaccinated and ١١ children (٣,٩%) were not sure about their vaccination status. While among the ١١٩ children who were not born in Khartoum, ٨٩ (٧٤,٨%) were vaccinated and ٢٥ children (٢١,٠%) were not vaccinated and the remaining ٤,٢% had their vaccination status unknown.

Table 4: Place of birth in relation to BCG vaccination. (n=399)

History of BCG	Place of birth					
	<u>Not born in May</u>		<u>Born in may</u>		<u>Total</u>	
	No	%	No	%	No	%
Yes	89	74,8	209	92,0	348	87,2
No	20	21,0	10	3,6	30	8,8
Unknown	0	0,0	11	3,9	11	3,0
Total	119	100	280	100	399	100

$$\chi^2 = 31,964$$

$$P. \text{ value} = .000$$

3.6.2. Mother education in relation to BCG vaccination:

Two hundreds and two of the mothers were illiterate (50.6%), 12.5% had been to Khalwa, 10.7 (26.8 %) were primary school graduate and only 10.0% (2.5) were secondary school and one university graduate (Table 10).

Table 10: Mother education in relation to BCG vaccination.
(n=399)

History of BCG	Mother education									
	<u>Secondary</u>		<u>Primary</u>		<u>Khalwa</u>		<u>Illiterate</u>		<u>Total</u>	
	No	%	No	%	No	%	No	%	No	%
Yes	36	90,0	94	87,9	44	88,0	174	86,2	348	87,2
No	3	7,5	10	9,3	5	10,0	17	8,4	35	8,8
Unknown	1	2,5	3	2,8	1	2,0	11	5,4	16	4,0
Total	40	100	107	100	50	100	202	100	399	100

3.7. Prevalence and Annual Risk of TB Infection (ARI):

Prevalence of infection: It is the percentage of individuals who show a positive reaction to the tuberculin test. Prevalence represents a cumulative experience of a population to recent and remote infection with M. tuberculosis. (1)

Annual Risk of Infection (ARI): (Incidence of Infection)

Is the percentage of the population under study who will be newly infected during the course of one year. It reflects the annual risk of being infected (or reinfected) in a given community. (1)

Every 1% of annual risk of infection is said to correspond to 10 new cases of smear positive pulmonary tuberculosis per year for 100,000 general populations. (1)

In this study the prevalence of Latent TB infection is

$$= \frac{\text{No. of positive reactors}}{\text{Total No. studied}} \times 100$$

$\frac{67}{399} \times 100 = 16\%$ (when positive is taken at 10mm for the vaccinated and at 10 for the non-vaccinated).

While the positivity among the children without scar at 10 mm: the prevalence of infection:

$$\frac{20}{113} \times 100 = 17.6\%$$

The children who react positive and have no BCG scar = 20 children.

The total children without scar = 113 children (Table 4).

The ARI is calculated from the WHO formula which is available at WHO website. (1)

The prevalence of infection and the mean age of the population in the study (5.4 years),

the year of the survey were the information needed to calculate the ARI.

The ARI calculated according to the WHO formula for the prevalence of 14% is = 2,02%.

From the ARI the estimated incidence of smear-positive TB and its 95% confidence interval using the Styblo-ratio is calculated as follows:

Styblo ratio: 1% ARI corresponds to an incidence of smear-positive TB of 0.1 per 100,000 populations. (1) (1')

So in this study the ARI is 2,02% and the estimated incidence of smear positive cases is:

100,9/100,000 population per year.

CHAPTER FOUR

DISCUSSION

This study carried out to determine the prevalence of Latent TB infection among the internally displaced school children in Mayo area in Khartoum through tuberculin survey at schools in children 6-9 years of age. The study included 416 children and 11 did not return for the reading of the Mantoux test, so the records of 405 children were analyzed. The advantages of using the prevalence and annual risk of infection, rather than the prevalence of the disease as epidemiological indicators are that infection is far more prevalent than disease, and it can be measured in children, as children when infected usually reflect exposure to an infectious adult with TB.

Tuberculin skin test is used in the diagnosis of tuberculosis in diseased patients; it is as well used to measure the prevalence of latent infection among populations through tuberculin surveys.

However the reaction to the tuberculin may also indicate infection with various non-tuberculous mycobacteria or vaccination with BCG.

The choice of study population for TB prevalence study would be unvaccinated children below 10 years of age in whom the prevalence of mycobacteria other than tuberculosis is minimum. But in countries like Sudan with universal BCG vaccination children with BCG can be included in tuberculin surveys as reported in the studies from India⁽¹⁾, Saudi Arabia⁽²⁾ and Turkey⁽³⁾, Hong Kong⁽⁴⁾. Moreover a study from India⁽⁵⁾ concluded that there was no significant difference in the prevalence of infection between children with BCG scar and those without BCG scar.

The age group 6-9 years is selected because it is the age when the BCG induced

reactivity of the tuberculin wanes and the acquired reactivity due to environmental mycobacteria is minimum as found in India^(44, 45).

The cutoff point for tuberculin positivity used in this study is 10 mm or more for the children not vaccinated with BCG, and 15 mm or more for the vaccinated. This level is chosen as it is recommended by CDC that according to their risk of TB children with 15 mm and more considered having TB infection even in children with low risk⁽⁴⁶⁾. The same was found in the study among refugees in Spain⁽⁴⁷⁾ and in a study from Turkey. Moreover Diab had chosen similar cutoff points in his study⁽⁴⁸⁾.

More males than females were included in this study with male to female ratio of 1,2:1,0 which is very near to the study by Diab⁽⁴⁸⁾ (male: females 1,23:1,0), while in Elnour's⁽⁴⁹⁾ survey male to female ratio was 1,00: 1,03.

Children included in this study were 6-9 years of age and the mean age was 7,4 years. Diab⁽⁴⁸⁾ studied the prevalence of TB infection among children with house hold contact in children 3 month to 6 years. And Mai⁽⁵⁰⁾ in her study about the BCG efficacy in children in East Nile province studied the 1-9 years children. While Hind⁽⁵¹⁾ in her tuberculin survey included children from 3 month up to 15 years old. This difference in the age groups studied might result in difference in prevalence of tuberculin reactions.

Although almost all the families were originally from the Southern and Western Sudan, most of the families have been residing in Mayo before the birth of their children involved in this study. And this was significant in that children born in Mayo had more chance of being vaccinated.

Most of the families in this study have no fixed monthly income; actually it was daily unstable income. And the majority has a total per month of less than 50,000 SD.

BCG Vaccination coverage among the study group is 87,2%, which is near that

achieved in Gabal Awlia locality in ٢٠٠٤ which was ٨١,٧%.

The Khartoum state BCG coverage for infants under one year in ٢٠٠٤ was ٨٢% and for Sudan in ٢٠٠٤ it was ٧١%.

Elnour^(٢١) in her survey reported ٨٣% with definite history of BCG vaccination and Elhasan^(٢٢) reported ٩٥% vaccination among her study population while Diab^(٢٣) reported ٨١,٣%.

Almost all the children in this study had had their BCG at birth or at two month of age with the first doses of DPT and OPV, and this is compatible with the national policy of the EPI.

BCG scar rate among the vaccinated was ٨١,٩% near to that reported by Elnour^(٢١) that three quarters of the vaccinated developed scar, while Elhasan^(٢٢) in her study reported ٧٢% scar rate among the vaccinated children.

Scar rate among the study group was ٧١,٧% which is similar to the finding of Diab (٧٠%) and that reported by Elhasan(٧٢%). And also comparable to the study in Iran^(٤١) of ٧١,٥%. However, this is much different from the situation found by Zaki^(٢٤) of only ٨,٧% scar positive among children in Tokar, Haya and Port Sudan in ١٩٩٤.

Regarding the tuberculin reaction among the study group, ٧٣% of the children in the study group had reactions less than ٥ mm which is appropriate to Elhasan^(٢٢) (٦٨,٨%) and is different from Elnour^(٢١) (٤٩%).

A study from India^(٤٢) found that ٧٠% of the children ٠-٩ years vaccinated with BCG elicited either no reaction or reaction less than ١٠mm. and in Iran^(٤١) ٦٨% of vaccinated were negative by ٤ years.

Almost one fifth of the children (١٩,٩%) in this study had tuberculin reactions more than ١٠mm.in contrast to Elnour^(٢١) (١١%) and far from that reported by Elhasan^(٢٢)

(2,0%); however this can be explained by the difference in age groups among the three studies. Moreover it can be due to difference in the populations studied i.e. the more than 10mm is more prevalent among the population in Mayo in comparison to East Nile Province.

The cutoff point for Latent TB infection in this study is 10mm or more for the non-vaccinated and 10mm and more for the vaccinated children. And so the infectivity is 14%. While among children without scar the infectivity is 14,6%. This does agree with Elsafi (14) in her study in Eastern Sudan in 2002 that reported less than 20% were tuberculin positive by 10 years. And this is comparable by the infectivity reported by Elnour(15) of 10,0%. Although Diab(16) reported prevalence of infection at 40,8% among the children with household TB contact.

In the study from Turkey (17) among school children from high TB burden population tuberculin positivity was 00%. In Nepal (18) it was 33%. Tuberculin positivity was 13% among immigrant children in Italy (19).

Among the children without BCG scar in this study infectivity is 14,6%, different from Zaki(20) who reported infectivity in non vaccinated children of 34% at 9 years. However Zaki cutoff point for positivity among his study group was 8mm. In Kenya, Bosman (21) found that 10mm or more among none vaccinated was 9,2%, in Ethiopia, Azbite (22) reported 23% of the children with BCG scar tested positive and 10,6% of children who did not have BCG scar tested positive for tuberculosis.

The prevalence of Latent TB infection among children with BCG scar in this study is 13,3% and among children without BCG scar is 14,6% and this has no statistical difference and is comparable to the study by Chadha (23) in India where the prevalence of infection was 11,8% among children without BCG scar and 10,6% among children

with scar and the difference was reported as insignificant.

When considering Latent TB infection in relation to age in this study, TB infection has increased prevalence with increased age. The difference in age between the age groups is small; however this result is consistent with Zaki^(٢٠١٦) and Elsafi^(٢٠١٦) that infectivity increases with age. Tuberculosis is more prevalent among males in adult and among females in children, but in this study gender is not related to Latent TB infection. This is similar to Elnour^(٢٠١٦) where gender difference did not affect tuberculin reactivity but Elnour believes that gender difference starts to appear at adolescence when social life and duties of males give more chance of exposure reflected in increased tuberculin reactivity and increased risk of infection among adolescents. .

It is known that TB risk of infection is increased among contacts of infectious adult; a fact which is well represented in this study and similar to the finding of Elnour^(٢٠١٦).

The BMI difference among the children in this study does not follow the prevalence of Latent TB infection. However Diab^(٢٠١٦) has found TB infection more prevalent among malnourished children. This can be attributed to the difference in age groups studied as malnutrition is more prevalent in children under ٥ years of age.

Most of the children were living in crowded environment, hence crowding represents a significant risk factor for Latent TB infection in this study. This in contrast to Diab^(٢٠١٦) who found domestic crowding has no remarkable effect in the spread of TB.

In this study the ARI is ٢,٠٢% and the estimated incidence of smear positive population is: ١٠٠,٩/١٠٠,٠٠٠.

And the national figures by the NTP of ARI of =١,٨% with ٩٠/١٠٠,٠٠٠ smear positive cases per year.

CONCLUSION

- Among the study group BCG vaccination is 87% which is comparable to the EPI figures.
- As BCG is routinely given at birth or two month, children born in Mayo have greater chance of having the vaccine and this is comparable to EPI figures.
- 91,7% of the studied population has BCG scar, and scar among the vaccinated is 81,9%.
- The prevalence of Latent TB infection is at 17,6% among children without BCG scar, (13,3%) among those with BCG scar and 14% for the whole group.
- The ARI is 2,0% which gives an incidence of 100,9/100,000 smear positive cases per year.
- The prevalence of latent TB infection increases with increased age.
- Domestic crowding increases the risk of Latent TB infection as tuberculosis is an infectious disease.
- There is no significant difference in the prevalence of Latent TB infection between males and females.
- Children in contact with TB patient are more likely to be infected.
- There was no significant relation to the prevalence of Latent TB infection in this study and the nutritional status.

RECOMMENDATIONS

- Internally displaced populations are among the high risk groups for tuberculosis; regular surveys and screening is recommended.
- Displaced children have greater chance of missing vaccination, so the EPI is recommended to insure BCG vaccination for the states with below average vaccination coverage.
- The innocent children in Mayo are living in crowded environment with poverty and poor socioeconomic condition, improvement of living environment and promotion of health among displaced population is highly recommended and urgently needed.
- Contacts investigations remain a basic strategy in TB control. This is strongly recommended among displaced populations.

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APPENDIX

University of Khartoum
Graduate College
Medical and Health Studies Board
Questionnaire

**Prevalence of Latent Tuberculosis Infection among the internally displaced
School Children in Mayo area, Khartoum**

Serial No:

Date:

1-Personal Data:

1.1. Name:

1.2. Address (home):

1.3. Gender: 1. Male 2.Female

1.4. Date of birth:

1.5. Place of birth:

1.6. Tribe:

1.7. State of origin:

1.8. Duration of stay in Mayo (camp) in years:

2-Socio- economic status:

2.1. Mother education:

1- Illiterate 2- Khalwa 3- Primary 4-Secondary 5- University

2.2. Mother occupation:

1- Government employee 2- Laborer 3- Without job 4- Others

2.3. Father education:

1- Illiterate 2- Khalwa 3- Primary 4-Secondary 5- University

2.4. Father occupation:

1- Government employee 2- Laborer 3-without job 4-others

2.5. Monthly family income:

3-Risk factors:

3.1. Number of rooms in the house:

3.2. Number of persons per room:

٣,٣. History of BCG vaccination: ١. Yes

٢. No

3,4. Age of the child when BCG given, in months:

3,5. Household contact with patient with cough for more than 1 month:

1. Yes

2. No

3,6. Contact with tuberculosis patient:

1- Household 2- Neighbor 3-No 4-don't know

3,7. If has contact with TB or chronic cough, duration of contact in months:

3,8. Weight of the child in Kgs:

3,9. Height of the child in cm:

3,10. BMI: 1) BMI < 3rd centile 2) BMI > 3rd centile

4-History and examination:

4,1. Has the child symptoms for more than 2 weeks: 1- Yes 2- No

4,2. What symptoms: 1-cough 2- Fever 3- Wt. loss 4- others

4,3. Symptoms of tuberculosis:

1. Yes 2. No

4,4. Is the child on treatment for more than 1 month? 1. Yes 2. No

4,5. What type of treatment?

4,6. Clinical examination: -----

5-Tuberculin Test: Date of test:

5,1. BCG scar present: 1. Yes 2. No

5,2. Mantoux reading:

1) < 5mm 2) 5-9mm 3) 10-14mm 4) 15-19mm 5) 20 and more

5,3. Tuberculosis infection: 1. Yes 2. No

